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Biochemistry

YY1 and c-Myc associate *in vivo* in a manner that depends on c-Myc levels

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ABSTRACT **The c-Myc oncoprotein has previously been shown to associate with transcription regulator YY1 and to inhibit its activity. We show herein that endogenous c-Myc and YY1 associate *in vivo* and that changes in c-Myc levels, which accompany mitogenic stimulation or differentiation of cultured cells, affect the ratio of free to c-Myc-associated YY1. We have also investigated the mechanism by which association with c-Myc inhibits YY1's ability to regulate transcription. c-Myc does not block binding of YY1 to DNA. However, protein association studies suggest that c-Myc interferes with the ability of YY1 to contact basal transcription proteins TATA-binding protein and TFIIB.**

The c-*myc* proto-oncogene encodes a ubiquitiously expressed nuclear phosphoprotein (1–3). Despite clear evidence that c-Myc is important in the control of cellular proliferation, differentiation, apoptosis, and transformation (1), the molecular mechanisms by which c-Myc functions are not completely understood.

c-Myc has DNA-binding, dimerization, and transactivations domains common to other transcriptional activators (1). c-Myc–Max heterodimers can activate the p53 (4), ECA39 (5), α-prothymosin (6), DHFR (7), and ornithine decarboxylase genes (8, 9). However, the number of known c-Myc–Max-regulated genes remains small, suggesting that important facets of c-Myc action remain uncharacterized. In addition, some mutants of c-Myc are defective in transformation ability but not in transcriptional activation ability (10), suggesting that functions other than transcriptional activation may be important for c-Myc function.

c-Myc can also suppress the expression of specific genes including the major histocompatibility complex class I antigens HLA-A2 (11) and HLA-C (12), cyclin D1 (13), integrin LFA-1 (14), adhesion receptor N-CAM (15), and transcription factor C/EBPα (16). c-Myc also represses its own transcription (17). No c-Myc–Max binding sites have been identified in the regulatory regions of these genes and the mechanism(s) by which Myc suppresses their transcription is poorly understood although for the C/EBPα and albumin genes c-Myc appears to act on initiator elements (10) .

We have shown (18) that c-Myc can physically associate *in vitro* and in the yeast two-hybrid system with transcription protein YY1. YY1 is a ubiquitiously expressed zinc finger protein (19–23) that functions as a transcriptional repressor, activator, or initiator, depending upon the context of its binding site. YY1 binding sites are widely distributed in many cellular and viral promoters (24). Association with c-Myc inhibits the transcriptional activating and repressing abilities of YY1 (18). We have suggested (18) that c-Myc may regulate transcription of YY1-dependent genes by modulating YY1 activity. Since regulation of YY1 activity could provide an additional mechanism for c-Myc-dependent transcriptional regulation, we have investigated the physiological relevance and molecular mechanism of this association.

METHODS

Antiserum Preparation. Murine c-Myc antiserum was generated by injecting bovine albumin serum (BSA) coupled to a synthetic peptide representing the C-terminal 13 amino acids of murine c-Myc into rabbits.

Plasmids Construction. Full-length YY1 cDNA, 1.8 kbp, was excised from pGEM-4Z-YY1 (21) by *Nco*I digestion, end-filled, and *Bam*HI digestion, and inserted into *Bam*HI and *Sma*I restriction sites of pCGN (25). The His-YY1 plasmid was constructed by ligating a *Kpn*I fragment from pCGN-YY1 into the pQE32 vector (Qiagen). A glutathione *S*-transferase (GST) fusion protein (Gst–Myc) was constucted by ligating a 600-bp PCR fragment of c-Myc, corresponding to amino acids 259–439, into the *Bam*HI and *Sma*I sites of pGEX-3X vector (26). The PCR fragment was generated using oligonucleotides that put a *Bam*HI site at the 5′ end.

Purification of Proteins. His-YY1 was expressed by isopropyl β-D-isothiogalactoside induction of bacteria containing the YY1 expression plasmid. Protein was purified by binding to a Ni-NTA resin (as described in Qiagen protocol). GST fusion proteins were expressed and purified on glutathione-agarose as described (27).

Coimmunoprecipitation. Approximately 2×10^7 M12, murine erythroleukemia (MEL), or NIH 3T3 cells were washed, resuspended in buffer X [50 mM Tris·HCl, pH 7.5/50 mM NaCl/7 mM $CaCl_2$/10 mM EDTA/5 mM DTT/0.5% Nonidet P-40/1 mM phenylmethylsulfonyl fluoride/pepstatin (20 μg/ml)/leupeptin (20 μg/ml)/aprotinin (20 μg/ml)], sonicated on ice, and centrifuged for 30 min at 15,800 *g* to obtain lysates used for coimmunoprecipitation. For M12 and MEL cells, lysate was precleared by incubating 20 min with protein A-Sepharose beads in buffer X. Lysate was kept on ice for 1 hr and incubated with anti-Myc antisera for 2 hr and then with protein A-Sepharose beads for 4 hr. Proteins bound to beads were resolved by SDS/PAGE and visualized by immunoblot analysis with anti-Myc polyclonal antiserum and anti-YY1 monoclonal antibody. One-tenth of each immunoprecipitate was used for the c-Myc blots and nine-tenths was used for the YY1 blots.

GST Assays. GST assays were performed as described (19). Association assays were done in buffer that had final conditions of 50 mM NaCl, 7 mM $CaCl_2$, BSA (10 mg/ml), 5 mM DTT, 1 mM phenylmethylsulfonyl fluoride, aprotinin (20 μg/ml), leupeptin (20 μg/ml), and pepstatin (20 μg/ml).

RESULTS

YY1 Associates with c-Myc in Mammalian Cells. We have shown (18) that c-Myc and YY1 could associate when they were ectopically expressed in yeast; however, to assess the biological relevance of the association, we wished to deter-

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Abbreviations: GST, glutathione *S*-transferase; TBP, TATA-binding protein.

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mine, using coimmunoprecipitation, if the two proteins were associated in mammalian cells. To establish immunoprecipitation conditions, crude cell lysates from Daudi cells and 293T cells (28) stably transfected with a CMV-YY1 expression vector were mixed. After incubation, c-Myc was immunoprecipitated from the mixture (Fig. 1*A*) using conditions that allowed association of c-Myc and YY1 as judged by the *in vitro* GST fusion protein assay (data not shown). Analysis of the c-Myc immunoprecipitates on immunoblots developed with a monoclonal antibody to YY1 (IG3α, a gift from T. Shenk, Princeton University) revealed a YY1 band (Fig. 1*B*, lane 2). Specificity was demonstrated by blocking with the 13-amino acid c-Myc peptide used to elicit the c-Myc antiserum (Fig. 1*B*, lane 3). Thus, these conditions immunoprecipitate c-Myc and YY1 that associate in lysates of mammalian cells.

Subsequently, we coimmunoprecipitated endogenous c-Myc and YY1 from M12, a murine B-cell lymphoma. Polyclonal antiserum raised to the C-terminal 13 amino acids of murine c-Myc was used for immunoprecipitation of M12 lysates and the immunoprecipitate was examined by immunoblot analysis. Fig. 2 (*left*), lanes 1 and 2, shows that anti-c-Myc but not preimmune serum immunoprecipitated c-Myc. Fig. 2 (*center*) shows that YY1 was coimmunoprecipitated by anti-c-Myc (lane 5) but not by preimmune serum (lane 4). The specificity of the YY1 band was established by developing parallel lanes of the blot with an isotype-matched control monoclonal antibody that did not show a YY1 band (Fig. 2 *right*). Since M12 cells express YY1 and c-Myc only from the endogenous genes, these results show that physiological levels of the two proteins allow their association *in vivo*.

The Amount of YY1 Associated with c-Myc Varies When c-Myc Levels Change. We reasoned that changes in c-Myc protein levels might regulate the ratio of free YY1 to c-Myc-associated YY1 in situations where overall YY1 levels remained unchanged. To test this hypothesis, we coimmunoprecipitated YY1 associated with c-Myc from 3T3 cells in which c-Myc is induced in response to serum stimulation (29, 30) and from MEL cells where c-Myc levels decrease upon differentiation in response to dimethyl sulfoxide (31). c-Myc, YY1, and YY1 associated with c-Myc were determined before and after the treatments to alter c-Myc levels. Fig. 3*A* shows that when quiescent 3T3 cells were treated with serum for 2 hr, c-Myc was strongly induced but YY1 levels did not change during this time (Fig. 3*B*). Measured by coimmunoprecipitation, the amount of YY1 associated with c-Myc also increased from undetectable to detectable amounts (Fig. 3*C*). Thus mitogenic stimulation induces c-Myc, resulting in association between YY1 and c-Myc and thus decreasing the amount of free YY1 available to regulate YY1-dependent genes. Similarly, when MEL cells were stimulated to differentiate in response to dimethyl sulfoxide, c-Myc levels decreased 75% and YY1

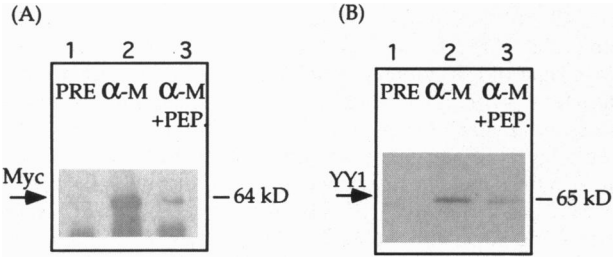

FIG. 1. c-Myc associates with YY1 in cell lysates containing exogenously expressed YY1. c-Myc was immunoprecipitated from a 1:1 mixture of whole cell lysates from Daudi cells and 293T cells transfected with CMV-YY1 using preimmune serum (Pre), polyclonal antiserum against the C-terminal 13 amino acids of human c-Myc (α-M) or anti-human c-Myc plus human c-Myc C-terminal peptide (α-M+pep). (*A*) Immunoprecipitate examined by immunoblot analysis with anti-human c-Myc. (*B*) Immunoprecipitate analyzed using monoclonal antibodies against YY1.

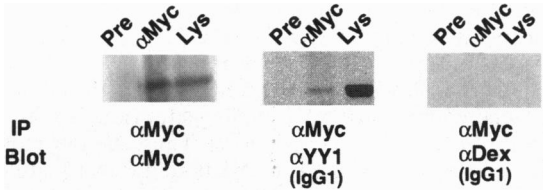

FIG. 2. c-Myc associates with endogenous YY1 in M12 cells. c-Myc was immunoprecipitated from M12 cell lysate using preimmune serum (Pre) or polyclonal antiserum raised against the C-terminal 13 amino acids of murine c-Myc (α-Myc); untreated lysate (Lys) was also electrophoresed as a control. Blots of the gel were developed as indicated. (*Left*) Polyclonal antiserum raised against the C-terminal 13 amino acids of mouse c-Myc. (*Center*) YY1 monoclonal antibody (IgG1). (*Right*) An isotype-matched control monoclonal antibody to dextran. α, Anti-.

associated with c-Myc decreased 62% although YY1 levels did not change (data not shown). These results support a model in which changes in c-Myc levels modulate the availability of active YY1.

YY1 Associated with c-Myc Can Still Bind YY1 Sites in DNA. We wished to explore the mechanism by which c-Myc inhibits the transcriptional activating and repressing activities of YY1 (18). To test the model that association with c-Myc abrogates the ability of YY1 to bind DNA, an electrophoretic mobility shift assay was performed using the YY1 site from the immunoglobulin heavy chain enhancer (μE1 site) (32) as a probe for binding of recombinant YY1 and bacterially produced GST–c-Myc. Increasing amounts of highly purified GST–c-Myc (259–439 amino acids) or GST, which was purified in parallel, were added with YY1 to binding reaction

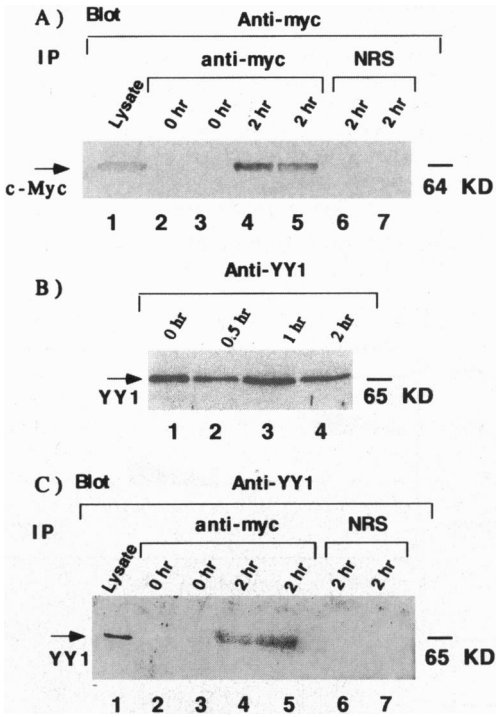

FIG. 3. YY1–c-Myc complexes increase when 3T3 cells are stimulated with serum. (*A*) Immunoblot developed with anti-c-Myc antiserum. Lanes: 1, lysate from serum-stimulated cells; 2 and 3, immunoprecipitates using anti-c-Myc antiserum from serum-starved cells; 3 and 4, immunoprecipitates using anti-c-Myc antiserum from cells 2 hr after adding serum; 6 and 7, immunoprecipitates from serum-treated cells using preimmune serum. (*B*) Immunoblot of cell lysates before and after serum stimulation developed with anti-YY1 antiserum. (*C*) Immunoblot developed with anti-YY1 antiserum. Lanes are identical to those in *A*.

mixtures (Fig. 4). In additional to the YY1–DNA complexes, a lower mobility complex specific to GST–c-Myc (lanes 1–3) but not GST (lanes 5–7) was also observed. When YY1 was omitted, no complexes were observed (lane 4). The complexes were competed by excess YY1 binding sites (lane 10) and not by excess c-Myc binding sites (lane 9). Thus, the low mobility complex corresponds to YY1–c-Myc bound to YY1 sites. We conclude that association with c-Myc does not block the ability of YY1 to bind DNA, although our data do not allow us to determine whether association with c-Myc alters the affinity of YY1 for its binding site.

Association of YY1 with the TATA-Binding Protein (TBP) and TFIIB Requires the Same Region of YY1 That Is Required for Association with c-Myc. Since association with c-Myc does not inhibit the ability of YY1 to bind DNA, we hypothesized that c-Myc may block YY1 action by inhibiting protein–protein associations between YY1 and other transcriptional proteins. YY1 is known to associate with two components of the basal transcription machinery, TBP and TFIIB (A. Berrier and K.C., unpublished results and ref. 33). Amino acids 201–343 of YY1 are necessary and amino acids 1–343 are sufficient for its association with c-Myc (18). We determined the region of YY1 required for association with TBP and TFIIB by using a GST fusion protein assay. Both TBP and TFIIB associated with full-length GST–YY-(1–414) but not GST alone (Fig. 5, lanes 2 and 7). C-terminal truncations of YY1 were then tested. GST–YY1-(1–343) still associates with TBP and TFIIB (Fig. 5, lanes 3 and 8), demonstrating that amino acids 344–414, which include three of the four zinc finger domains, are not required for the association. However, GST–YY1-(1–201) fails to associate with either TBP or TFIIB (lane 4 and 9), demonstrating that YY1 amino acids 201–343 are required for association with TBP and TFIIB. GST–YY1-(201–343) associates with TBP but not with TFIIB (lanes 5 and 10), demonstrating that amino acids 201–343 are sufficient for YY1 association with TBP but are not sufficient for association with TFIIB. Thus, the same region of YY1-(201–343) is required for association with c-Myc, TBP, and TFII-B (Fig. 5*C*), suggesting that association with c-Myc blocks the ability of YY1 to associate with TBP or TFIIB.

DISCUSSION

Inhibition of YY1 Activity by c-Myc. The association between YY1 and TFII-B has been shown to be functionally

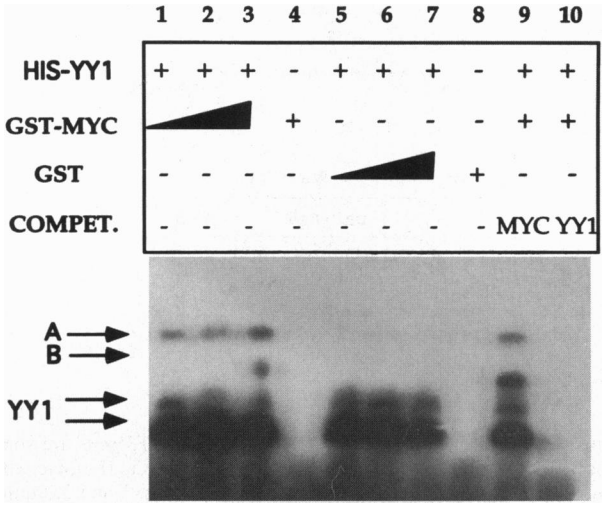

FIG. 4. YY1–c-Myc complexes bind to YY1 sites on DNA. Electrophoretic mobility shift assay using a double-stranded oligonucleotide probe corresponding to the IgH YY1 site (32) and highly purified bacterially expressed His-YY1, GST–Myc, and control GST. Double-stranded oligonucleotide competitors corresponding to the YY1 site or consensus Myc site (1) were added in 100-fold molar excess.

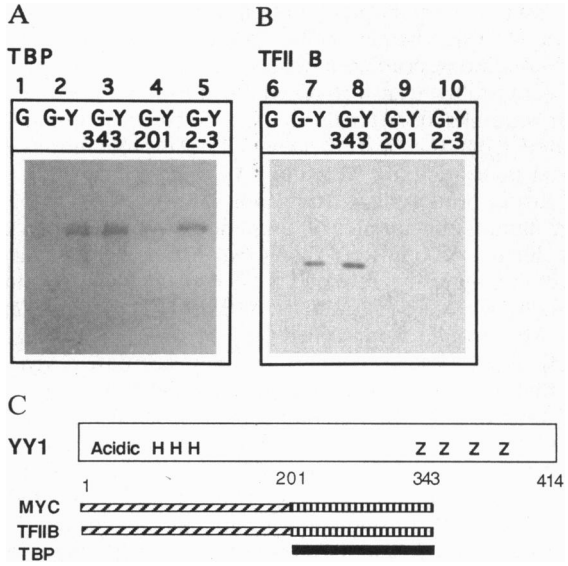

FIG. 5. Regions of YY1 required for association with TBP and TFIIB. GST binding assays of [^{35}S]Met-labeled TBP (*A*) and TFIIB (*B*) to GST (G), GST–YY1 (G-Y), GST–YY1-(1–343) (G-Y 343), GST–YY1-(1–201) (G-Y 201), and GST–YY1-(201–343) (G-Y 2–3). All GST fusion proteins were present at similar levels, as judged by Coomassie-stained SDS/PAGE gels (data not shown). (*C*) Regions of YY1 required for protein association are shown. Solid box is sufficient; individual hashed boxes are necessary but not sufficient.

important for YY1 to initiate transcription *in vitro* (33). It is reasonable to assume that associations with TBP and/or TFIIB are also important for the ability of YY1 bound at upstream sites to activate or repress transcription, although this has not been shown experimentally. Our data show that amino acids 201–343 of YY1, which are required for association with c-Myc (18), are also required for association with TBP and TFIIB. Since c-Myc association requires the same YY1 region as TFIIB and TBP, it follows that association with c-Myc is likely to block the transcriptional activation and/or repression activity of YY1 by interfering with functionally important YY1–TFIIB and/or YY1–TBP associations.

We have been unable demonstrate that c-Myc competes with TBP or TFIIB for association with YY1 because TBP and TFIIB also bind c-Myc (A.S. and J. Yu, unpublished results). However, adenovirus E1A has been shown to compete with c-Myc for association with YY1 and amino acids 201–343 are part of the region of YY1 required for the association with E1A protein (27). Therefore, by analogy, c-Myc probably competes with TBP and TFIIB for association with YY1. To date, all proteins that associate with YY1 require amino acids 201–343, thus defining this region as a protein association domain of YY1. By associating with YY1 via this domain, c-Myc may block association of YY1 with many functionally important proteins, although additional experiments will be necessary to test this hypothesis. A related mechanism has been suggested for c-Myc's inhibition of TFIII activity–i.e., that it blocks association between TFIII and USF (34).

c-Myc also associates with TBP (35, 36) and with TFIIB (A. Berrier and K.C., unpublished results). The N-terminal region of c-Myc (amino acids 1–179) associates with TBP, distinct from the C-terminal region of c-Myc (amino acids 250–434), required for association with YY1 (18, 35). Thus ternary complexes of TBP, c-Myc, and YY1 are theoretically possible. Thus, these facts suggest a model in which YY1, bound to an upstream site, normally makes contacts with TBP and/or TFIIB, which are required for YY1 to activate or repress transcription. However, when YY1–c-Myc binds, normal YY1 contacts with TBP and/or TF-IIB are blocked, altering the

preinitiation complex and inhibiting YY1 activity. In addition, TBP may associate with c-Myc in the c-Myc–YY1 complex. This association could stabilize an altered arrangement of proteins and might play a role in the ability of c-Myc to inhibit YY1. A similar model has recently been demonstrated for the even-skipped protein in *Drosophila* that associates with TBP (37) and represses transcription by preventing TBP from binding DNA (38).

c-Myc Levels and YY1-Dependent Genes. In addition to YY1, c-Myc also associates with Max, TBP (35, 36), p107 (39), TFIII (40), Rb (41), and TFIIB (A. Berrier and K.C., unpublished data). In addition to c-Myc, YY1 associates with TBP, TFIIB, Sp1 (42, 43), nucleolar protein B23 (44), p300 (45), and transcription factor TFE3 (A.S. and K.C., unpublished data); YY1 has also been identified as a nuclear matrix-associated protein (46). In spite of the complicated possible associations in the nucleus, we have shown that physiological changes in c-Myc are sufficient to alter the amount of YY1 associated with c-Myc. Thus, changes in c-Myc levels could alter the amount of YY1 enough to change expression of YY1-dependent genes. The growing list of YY1-dependent genes currently includes 17 cellular genes and 8 viral genes, including ubiquitously expressed genes (21, 34, 47–49), tissue-specific genes (22, 33, 50–52), and protooncogenes c-*fos* (53) and c-*myc* (32, 54). YY1 binding sites are also found in protooncogene N-*ras* and the cell-cycle-regulated E2F1 promoter (55, 56). Altered expression of YY1-dependent genes could have important effects on cell growth and, thus, could be responsible for some effects of c-Myc.

The most dramatic changes in c-Myc levels are associated with tumors where c-*myc* gene expression is deregulated due to chromosomal translocation, gene amplification, or retroviral insertion (57–60). The aberrantly high levels of c-Myc in tumors is likely to cause a significant change in expression of YY1-dependent genes. It will be interesting to determine whether any genes that are differentially expressed in tumors with elevated levels of c-Myc lack c-Myc–Max sites and are YY1-dependent.

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1. Marcu, K., Bossone, S. & Patel, A. (1992) *Annu. Rev. Biochem.* **61,** 809–860.
2. Luscher, B. & Eisenman, R. (1990) *Genes Dev.* **4,** 2025–2035.
3. Evans, G. I. & Littlewood, T. D. (1993) *Curr. Opin. Genet. Dev.* **3,** 44–49.
4. Reisman, D., Elkind, N. B., Roy, B., Beamon, J. & Rotter, V. (1993) *Cell Growth Differ.* **4,** 57–65.
5. Benvenisty, N., Leder, A. & Leder, P. (1992) *Genes Dev.* **6,** 2513–2523.
6. Gaubatz, S., Meichle, A. & Eilers, M. (1994) *Mol. Cell. Biol.* **14,** 3853–3862.
7. Mai, S. & Jalava, A. (1994) *Nucleic Acids Res.* **22,** 2264–2273.
8. Vincent, C. K., Gualberto, A., Patel, C. V. & Walsh, K. (1993) *Mol. Cell. Biol.* **13,** 1264–1272.
9. Bello-Fernandez, C., Packham, G. & Cleveland, J. L. (1993) *Proc. Natl. Acad. Sci. USA* **90,** 7804–7808.
10. Li, L. H., Nerlov, C., Prendergast, G., MacGregor, D. & Ziff, E. B. (1994) *EMBO J.* **13,** 4070–4079.
11. Koller, B. H. & Orr, H. T. (1985) *J. Immunol.* **134,** 2727–2733.
12. Tibensky, D. & Delovitch, T. L. (1990) *Immunogenetics* **32,** 210–213.
13. Philipp, A., Schneider, A., Vasrik, I., Finke, K., Xiong, Y., Beach, D., Alitalo, K. & Eilers, M. (1994) *Mol. Cell. Biol.* **14,** 4032–4043.
14. Inghirami, G., Grignani, F., Sternas, L., Lombardi, L., Knowles, D. M. & Dalla, F. R. (1990) *Science* **250,** 682–686.
15. Barton, C. H., A., M. D. & Walsh, F. S. (1990) *Biochem. J.* **268,** 161–168.
16. Christy, R. J., Kaestner, K. H., Geiman, D. E. & Lane, M. D. (1991) *Proc. Natl. Acad. Sci. USA* **88,** 2593–2597.
17. Grignani, F., Lombardi, L., Inghirami, G., Sternas, L., Cechova, K. & R., D.-F. (1990) *EMBO J.* **9,** 3913–3922.
18. Shrivastava, A., Saleque, S., Kalpana, G., Goff, S., Artandi, S. & Calame, K. (1993) *Science* **262,** 1889–1892.
19. Flanagan, J. R., Becker, K. G., Ennist, D. L., Gleason, S. L., Driggers, P. H., Levi, B. Z., Appella, E. & Ozato, K. (1992) *Mol. Cell. Biol.* **12,** 38–44.
20. Chen, S., Mills, L., Perry, R., Riddle, S., Wobig, R., Lown, R. & Millette, R. (1992) *J. Virol.* **66,** 4304–4314.
21. Hariharan, N., Kelley, D. E. & Perry, R. P. (1991) *Proc. Natl. Acad. Sci. USA* **88,** 9799–9803.
22. Park, K. & Atchison, M. L. (1991) *Proc. Natl. Acad. Sci. USA* **88,** 9804–9808.
23. Shi, Y., Seto, E., Chang, L. S. & Shenk, T. (1991) *Cell* **67,** 377–388.
24. Shrivastava, A. & Calame, K. (1994) *Nucleic Acids Res.* **22,** 5152–5155.
25. Tanaka, M. & Herr, W. (1990) *Cell* **60,** 375–386.
26. Smith, D. & Johnson, K. (1988) *Gene* **67,** 31–40.
27. Artandi, S. & Calame, K. (1993) *Methods Mol. Genet.* **1,** 267–279.
28. Pear, W. S., Nolan, G. P., Scott, M. & Baltimore, D. (1993) *Proc. Natl. Acad. Sci. USA* **90,** 8392–8396.
29. Greenberg, M. E. & Ziff, E. B. (1984) *Nature (London)* **311,** 433–438.
30. Bird, R. C., Kung, T. Y., Wu, G. & Young-White, R. (1990) *Biochem. Cell. Biol.* **68,** 858–862.
31. Lachman, H. M. & Skoultchi, A. I. (1984) *Nature (London)* **310,** 592–594.
32. Riggs, K. J., Merrell, K. T., Wilson, G. & Calame, K. (1991) *Mol. Cell. Biol.* **11,** 1765–1769.
33. Usheva, A. & Shenk, T. (1994) *Cell* **76,** 1115–1121.
34. Atchison, M. L., Meyuhas, O. & Perry, R. P. (1989) *Mol. Cell. Biol.* **9,** 2067–2074.
35. Hateboer, G., Timmers, H. T., Rustgi, A. K., Billaud, M., van't Veer, L. J. & Bernards, R. (1993) *Proc. Natl. Acad. Sci. USA* **90,** 8489–8493.
36. Maheswaran, S., Lee, H. & Sonenshein, G. E. (1994) *Mol. Cell. Biol.* **14,** 1147–1152.
37. Um, M., Li, C. & Manley, J. (1995) *Mol. Cell. Biol.* **15,** 5007–5016.
38. Austin, R. & Biggin, M. (1995) *Mol. Cell. Biol.* **15,** 4683–4693.
39. Gu, W., Bhatia, K., Magrath, I. T., Dang, C. V. & Dalla-Favera, R. (1994) *Science* **264,** 251–254.
40. Roy, A. L., Carruthers, C., Gutjahr, T. & Roeder, R. G. (1993) *Nature (London)* **365,** 359–361.
41. Rustigi, A., Dyson, N. & Bernards, R. (1991) *Nature (London)* **352,** 541–544.
42. Lee, J. S., Galvin, K. M. & Shi, Y. (1993) *Proc. Natl. Acad. Sci. USA* **90,** 6145–6149.
43. Seto, E., Lewis, B. & Shenk, T. (1993) *Nature (London)* **365,** 462–464.
44. Inouye, C. J. & Seto, E. (1994) *J. Biol. Chem.* **269,** 6506–6510.
45. Lee, J. S., Galvin, K. M., See, R. H., Eckner, R., Livingston, D., Moran, E. & Shi, Y. (1995) *Genes Dev.* **9,** 1188–1198.
46. Guo, B., Odgren, P., van Wijnen, A., Last, T., Nickerson, J., Penman, S., Lian, J., Stein, J. & Stein, G. (1995) *Proc. Natl. Acad. Sci. USA* **92,** 10526–10530.
47. Chung, S. & Perry, R. P. (1993) *Nucleic Acids Res.* **21,** 3301–3308.
48. Farnham, P. & Means, A. (1990) *Mol. Cell. Biol.* **10,** 1390–1398.
49. Meyuhas, O. & Klein, A. (1989) *J. Biol. Chem.* **265,** 11465–11473.
50. Lee, T. C., Shi, Y. & Schwartz, R. (1992) *Proc. Natl. Acad. Sci. USA* **89,** 9814–9818.
51. Meier, V. S. & Groner, B. (1994) *Mol. Cell. Biol.* **14,** 128–137.
52. Peters, B., Merezhinskaya, N., Diffley, J. F. & Noguchi, C. T. (1993) *J. Biol. Chem.* **268,** 3430–3437.
53. Natesan, S. & Gilman, M. Z. (1993) *Genes Dev.* **7,** 2497–2509.
54. Riggs, K. J., Saleque, S., Wong, K. K., Merrell, K. T., Lee, J. S., Shi, Y. & Calame, K. (1993) *Mol. Cell. Biol.* **13,** 7487–7495.
55. Bauknecht, T., Angel, P., Royer, H. D. & zur, H. H. (1992) *EMBO J.* **11,** 4607–4617.
56. Hsiao, K.-M., McMahon, S. & Farnham, P. (1994) *Genes Dev.* **8,** 1526–1537.
57. Cole, M. D. (1986) *Annu. Rev. Genet.* **20,** 361–384.
58. Cory, S. (1986) *Adv. Cancer Res.* **17,** 189–234.
59. Kelly, K. & Siebenlist, U. (1986) *Annu. Rev. Immunol.* **4,** 317–338.
60. Marcu, K. B. (1987) *Bioessays* **6,** 28–32.